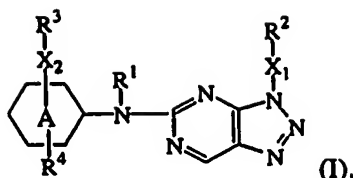


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Claims

1. A compound of formula



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl;

R^1 represents hydrogen; aryl; formyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyl;

C_{1-6} alkyloxycarbonyl; C_{1-6} alkyl substituted with formyl, C_{1-6} alkylcarbonyl,

C_{1-6} alkyloxycarbonyl, C_{1-6} alkylcarbonyloxy; or C_{1-6} alkyloxy C_{1-6} alkylcarbonyl

optionally substituted with C_{1-6} alkyloxycarbonyl;

X_1 represents a direct bond; $-(CH_2)_{n3}-$ or $-(CH_2)_{n4}-X_{1a}-X_{1b}-$;

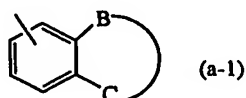
with n_3 representing an integer with value 1, 2, 3 or 4;

with n_4 representing an integer with value 1 or 2;

with X_{1a} representing O, C(=O) or NR^5 ; and

with X_{1b} representing a direct bond or C_{1-2} alkyl;

R^2 represents C_{3-7} cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula



wherein $-B-C-$ represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$ (b-1);

$-CH_2-CH_2-CH_2-CH_2-$ (b-2);

$-X_3-CH_2-CH_2-(CH_2)_n-$ (b-3);

$-X_3-CH_2-(CH_2)_n-X_3-$ (b-4);

$-X_3-(CH_2)_n-CH=CH-$ (b-5);


$-CH=N-X_3-$ (b-6);

with X_3 representing O or NR^5 ;

n representing an integer with value 0, 1, 2 or 3;

n' representing an integer with value 0 or 1;

wherein said R^2 substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C_{1-6} alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy,

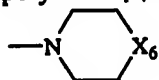
- C_{1-4} alkyloxy C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; C_{2-6} alkenyl or C_{2-6} alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy,
- C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; polyhalo- C_{1-6} alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; C_{1-6} alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; polyhalo C_{1-6} alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-C(=O)-NR^6R^7$, $-NR^5-C(=O)-NR^6R^7$, $-S(=O)_{n1}-R^8$ or $-NR^5-S(=O)_{n1}-R^8$; C_{1-6} alkylthio; polyhalo C_{1-6} alkylthio; C_{1-6} alkyloxycarbonyl; C_{1-6} alkylcarbonyloxy; C_{1-6} alkylcarbonyl; polyhalo C_{1-6} alkylcarbonyl; cyano; carboxyl; aryloxy; arylthio; arylcarbonyl; aryl C_{1-4} alkyl; aryl C_{1-4} alkyloxy; NR^6R^7 ; $C(=O)NR^6R^7$; $-NR^5-C(=O)-NR^6R^7$; $-NR^5-C(=O)-R^5$; $-S(=O)_{n1}-R^8$; $-NR^5-S(=O)_{n1}-R^8$; $-S-CN$; $-NR^5-CN$; oxazolyl optionally substituted with C_{1-4} alkyl; imidazolyl optionally substituted with C_{1-4} alkyl; or
- $-(CH_2)_{n2}-X_4-(CH_2)_{n2}-N$  X_5
- substituted with C_{1-4} alkyl; or
- with n_2 representing an integer with value 0, 1, 2, 3 or 4;
- with X_4 representing O, NR^5 or a direct bond;
- with X_5 representing O, CH_2 , $CHOH$, $CH-N(R_5)_2$, NR^5 or $N-C(=O)-C_{1-4}$ alkyl;
- X_2 represents a direct bond; $-NR^1-$; $-NR^1-(CH_2)_{n3}-$; $-O-$; $-O-(CH_2)_{n3}-$; $-C(=O)-$; $-C(=O)-(CH_2)_{n3}-$; $-C(=O)-NR^5-(CH_2)_{n3}-$; $-C(=S)-$; $-S-$; $-S(=O)_{n1}-$; $-(CH_2)_{n3}-$; $-(CH_2)_{n4}-X_{1a}-X_{1b}-$; $-X_{1a}-X_{1b}-(CH_2)_{n4}-$; $-S(=O)_{n1}-NR^5-(CH_2)_{n3}-NR^5-$; or $-S(=O)_{n1}-NR^5-(CH_2)_{n3}-$;
- R^3 represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, or a 9-or 10-membered bicyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said R^3 substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C_{1-6} alkyl optionally substituted with at least

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- one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkylthio; polyhaloC₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhaloC₁₋₆alkylcarbonyl; cyano; carboxyl; NR⁶R⁷; C(=O)NR⁶R⁷; -NR⁵-C(=O)-NR⁶R⁷; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R⁸; -NR⁵-S(=O)_{n1}-R⁸; -S-CN;
- NR⁵-CN; or $-(CH_2)_{n2}-X_4-(CH_2)_{n2}-N \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} X_5$; and in case R³ represents a saturated or a partially saturated 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said R³ may also be substituted with at least one oxo;
- R⁴ represents hydrogen; halo; hydroxy; C₁₋₄alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -NR⁵-C(=O)-NR⁹R¹⁰, -S(=O)_{n1}-R¹¹ or -NR⁵-S(=O)_{n1}-R¹¹; C₂₋₄alkenyl or C₂₋₄alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -NR⁵-C(=O)-NR⁹R¹⁰, -S(=O)_{n1}-R¹¹ or -NR⁵-S(=O)_{n1}-R¹¹; polyhaloC₁₋₃alkyl; C₁₋₄alkyloxy optionally substituted with carboxyl; polyhaloC₁₋₃alkyloxy; C₁₋₄alkylthio; polyhaloC₁₋₃alkylthio; C₁₋₄alkyloxycarbonyl; C₁₋₄alkylcarbonyloxy; C₁₋₄alkylcarbonyl; polyhaloC₁₋₄alkylcarbonyl; nitro; cyano; carboxyl; NR⁹R¹⁰; C(=O)NR⁹R¹⁰; -NR⁵-C(=O)-NR⁹R¹⁰; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R¹¹; -NR⁵-S(=O)_{n1}-R¹¹; -S-CN; or -NR⁵-CN;
- R⁵ represents hydrogen, C₁₋₄alkyl or C₂₋₄alkenyl;
- R⁶ and R⁷ each independently represent hydrogen; cyano; C₁₋₆alkylcarbonyl optionally substituted with C₁₋₄alkyloxy or carboxyl; C₁₋₆alkyloxycarbonyl; C₃₋₇cycloalkylcarbonyl; adamantanylcabonyl; C₁₋₄alkyloxyC₁₋₄alkyl;

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C₁₋₄alkyl substituted with C₁₋₄alkyl-NR⁵-; C₁₋₆alkyl optionally substituted with at least one substituent selected from halo, hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, polyhaloC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR^{6a}R^{7a}, C(=O)NR^{6a}R^{7a} or



; with X₆ representing O, CH₂, CHOH, CH-N(R₅)₂, NR⁵ or

5 N-C(=O)-C₁₋₄alkyl;

R^{6a} and R^{7a} each independently represent hydrogen; C₁₋₄alkyl or C₁₋₄alkylcarbonyl;

R⁸ represents C₁₋₄alkyl optionally substituted with hydroxy; polyhaloC₁₋₄alkyl or NR⁶R⁷;

R⁹ and R¹⁰ each independently represent hydrogen; C₁₋₆alkyl; cyano; C₁₋₆alkylcarbonyl;

10 C₁₋₄alkyloxyC₁₋₄alkyl; or C₁₋₄alkyl substituted with C₁₋₄alkyl-NR⁵-;

R¹¹ represents C₁₋₄alkyl or NR⁹R¹⁰;

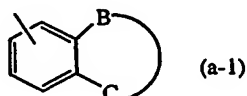
n₁ represents an integer with value 1 or 2;

aryl represents phenyl or phenyl substituted with at least one substituent selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl or

15 polyhaloC₁₋₆alkyloxy.

2. A compound according to claim 1 wherein

R² represents C₃₋₇cycloalkyl; phenyl or a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; or a radical
20 of formula



wherein -B-C- represents a bivalent radical of formula

-CH₂-CH₂-CH₂- (b-1);

-CH₂-CH₂-CH₂-CH₂- (b-2);

25 -X₃-CH₂-CH₂-(CH₂)_n- (b-3);

-X₃-CH₂-(CH₂)_n-X₃- (b-4);

-X₃-(CH₂)_n-CH=CH- (b-5);

with X₃ representing O or NR⁵;

n representing an integer with value 0, 1, 2 or 3;

30 n' representing an integer with value 0 or 1;

wherein said R² substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷,

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$-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{NR}^5-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{S}(=\text{O})_{n1}-\text{R}^8$ or $-\text{NR}^5-\text{S}(=\text{O})_{n1}-\text{R}^8$; C_{2-6} alkenyl
 or C_{2-6} alkynyl, each optionally substituted with at least one substituent selected from
 hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl,
 C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{NR}^5-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{S}(=\text{O})_{n1}-\text{R}^8$ or
 5 $-\text{NR}^5-\text{S}(=\text{O})_{n1}-\text{R}^8$; polyhalo C_{1-6} alkyl; C_{1-6} alkyloxy optionally substituted with
 carboxyl; polyhalo C_{1-6} alkyloxy; C_{1-6} alkylthio; polyhalo C_{1-6} alkylthio;
 C_{1-6} alkyloxycarbonyl; C_{1-6} alkylcarbonyloxy; C_{1-6} alkylcarbonyl;
 polyhalo C_{1-6} alkylcarbonyl; cyano; carboxyl; NR^6R^7 ; $\text{C}(=\text{O})\text{NR}^6\text{R}^7$;
 $-\text{NR}^5-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$; $-\text{NR}^5-\text{C}(=\text{O})-\text{R}^5$; $-\text{S}(=\text{O})_{n1}-\text{R}^8$; $-\text{NR}^5-\text{S}(=\text{O})_{n1}-\text{R}^8$; $-\text{S}-\text{CN}$;
 10 $-\text{NR}^5-\text{CN}$; or $-(\text{CH}_2)_{n2}-\text{X}_4-(\text{CH}_2)_{n2}-\text{N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{X}_5$

with $n2$ representing an integer with value 0, 1, 2, 3 or 4;

with X_4 representing O, NR^5 or a direct bond;

with X_5 representing O or NR^5 ;

X_2 represents a direct bond; $-\text{NR}^1-$; $-\text{O}-$; $-\text{C}(=\text{O})-$; $-\text{C}(=\text{S})-$; $-\text{S}-$; $-\text{S}(=\text{O})_{n1}-$; $-(\text{CH}_2)_{n3}-$; or

15 $-(\text{CH}_2)_{n4}-\text{X}_{1a}-\text{X}_{1b}-$;

R^3 represents a 5- or 6-membered monocyclic heterocycle containing at least one
 heteroatom selected from O, S or N, wherein said R^3 substituent, where possible,
 may optionally be substituted with at least one substituent selected from halo;
 hydroxy; C_{1-6} alkyl optionally substituted with at least one substituent selected from
 20 hydroxy, cyano, carboxyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl,
 C_{1-4} alkylcarbonyloxy, NR^6R^7 , $-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{NR}^5-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{S}(=\text{O})_{n1}-\text{R}^8$ or
 $-\text{NR}^5-\text{S}(=\text{O})_{n1}-\text{R}^8$; C_{2-6} alkenyl or C_{2-6} alkynyl, each optionally substituted with at
 least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy,
 C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, NR^6R^7 ,
 25 $-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{NR}^5-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$, $-\text{S}(=\text{O})_{n1}-\text{R}^8$ or $-\text{NR}^5-\text{S}(=\text{O})_{n1}-\text{R}^8$;
 polyhalo C_{1-6} alkyl; C_{1-6} alkyloxy optionally substituted with carboxyl;
 polyhalo C_{1-6} alkyloxy; C_{1-6} alkylthio; polyhalo C_{1-6} alkylthio; C_{1-6} alkyloxycarbonyl;
 C_{1-6} alkylcarbonyloxy; C_{1-6} alkylcarbonyl; polyhalo C_{1-6} alkylcarbonyl; cyano;
 carboxyl; NR^6R^7 ; $\text{C}(=\text{O})\text{NR}^6\text{R}^7$; $-\text{NR}^5-\text{C}(=\text{O})-\text{NR}^6\text{R}^7$; $-\text{NR}^5-\text{C}(=\text{O})-\text{R}^5$;

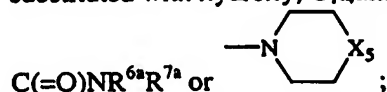
30 $-\text{S}(=\text{O})_{n1}-\text{R}^8$; $-\text{NR}^5-\text{S}(=\text{O})_{n1}-\text{R}^8$; $-\text{S}-\text{CN}$; $-\text{NR}^5-\text{CN}$; or $-(\text{CH}_2)_{n2}-\text{X}_4-(\text{CH}_2)_{n2}-\text{N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{X}_5$;

and in case R^3 represents a saturated 5- or 6-membered monocyclic heterocycle
 containing at least one heteroatom selected from O, S or N, said R^3 may also be
 substituted with at least one oxo;

R^5 represents hydrogen or C_{1-4} alkyl;

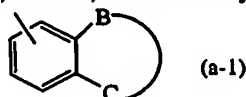
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R^6 and R^7 each independently represent hydrogen; cyano; C_{1-6} alkylcarbonyl; C_{1-4} alkyloxy C_{1-4} alkyl; C_{1-4} alkyl substituted with C_{1-4} alkyl- NR^5 -; C_{1-6} alkyl optionally substituted with hydroxy, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyloxy, NR^6R^7 ,



5 R^8 represents C_{1-4} alkyl, polyhalo C_{1-4} alkyl or NR^6R^7 .

3. A compound as claimed in claim 1 wherein ring A represents phenyl; R^1 represents hydrogen or C_{1-6} alkyl; X_1 represents a direct bond or $-(CH_2)_{n3}$ -; R^2 represents C_{3-7} cycloalkyl; phenyl; a 6-membered monocyclic heterocycle containing at least one
10 heteroatom selected from O, S or N; benzoxazolyl; or a radical of formula



wherein $-B-C-$ represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$ (b-1);

$-X_3-CH_2-(CH_2)_n-X_3-$ (b-4);

15 $-CH=N-X_3-$ (b-6);

with X_3 representing O or NR^5 ;

n representing an integer with value 1;

wherein said R^2 substituent, where possible, may optionally be substituted with at least one substituent, in particular with 1 or 2 substituents selected from halo; C_{1-6} alkyl
20 optionally substituted with at least one substituent selected from hydroxy, cyano, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyloxy, NR^6R^7 or $-C(=O)-NR^6R^7$; polyhalo C_{1-6} alkyl; C_{1-6} alkyloxy optionally substituted with C_{1-4} alkyloxy; C_{1-6} alkylthio; C_{1-6} alkyloxycarbonyl; cyano; arylthio; aryloxy; arylcarbonyl; NR^6R^7 ; $C(=O)NR^6R^7$; $-S(=O)_{n1}-R^8$; or imidazolyl optionally substituted with C_{1-4} alkyl;
25 X_2 represents a direct bond; $-NR^1$ -; $-O-(CH_2)_{n3}$ -; $-C(=O)-$; $-C(=O)-NR^5-(CH_2)_{n3}$ -; $-(CH_2)_{n3}$ -; or $-S(=O)_{n1}-NR^5-(CH_2)_{n3}-NR^5$ -; R^3 represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said R^3 substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C_{1-6} alkyl; or NR^6R^7 ; and in case R^3
30 represents a saturated or a partially saturated 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said R^3 may also be substituted with at least one oxo; R^4 represents hydrogen; nitro or carboxyl; R^5 represents hydrogen; R^6 and R^7 each independently represent hydrogen; cyano; C_{1-6} alkylcarbonyl optionally substituted with C_{1-4} alkyloxy; C_{1-6} alkyloxycarbonyl;

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C₃₋₇cycloalkylcarbonyl; adamantanylcabonyl; or C₁₋₆alkyl; R⁸ represents NR⁶R⁷; n1 represents an integer with value 2; aryl represents phenyl.

4. A compound as claimed in any one of claims 1 to 3 wherein ring A is phenyl; R¹ is hydrogen; X₁ is a direct bond or -(CH₂)_{n3}-; R² is indanyl; 2,3-dihydro-1,4-benzodioxanyl; phenyl optionally being substituted with 1 or 2 substituents each independently being selected from C₁₋₆alkyl which may optionally be substituted with hydroxy, cyano, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR⁶R⁷ or C(=O)NR⁶R⁷; C₁₋₆alkyloxy; halo; polyhaloC₁₋₆alkyl which may optionally be substituted with hydroxy, cyano, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR⁶R⁷ or C(=O)NR⁶R⁷; cyano; NR⁶R⁷; C(=O)NR⁶R⁷; -S(=O)_{n1}-R⁸; X₂ is direct bond; -NR¹-; -O-(CH₂)_{n3}-; -C(=O)-; -C(=O)-NR⁵-(CH₂)_{n3}-; or -(CH₂)_{n3}-; R³ is tetrazolyl; piperazinyl; imidazolyl; oxazolyl; pyrimidinyl; thiazolyl; triazolyl; pyridyl; piperidinyl, pyrazinyl; pyrazolyl or morpholinyl; said rings representing R³ may optionally be substituted with one substituent selected from C₁₋₆alkyl; NR⁶R⁷; hydroxy; halo; and in case R³ represents a saturated or a partially saturated ring system, said R³ may also be substituted with at least one oxo; R⁴ is hydrogen; R⁶ and R⁷ each independently represent hydrogen; cyano; C₁₋₆alkylcarbonyl optionally substituted with C₁₋₄alkyloxy; C₁₋₆alkyloxycarbonyl; C₃₋₇cycloalkylcarbonyl; or C₁₋₆alkyl; R⁸ represents NR⁶R⁷.
5. A compound as claimed in any one of claims 1 to 4 wherein the R³ substituent is linked to ring A in meta position compared to the NR¹ linker.
6. A compound as claimed in any one of claims 1 to 4 wherein the R³ substituent is linked to ring A in para position compared to the NR¹ linker.
7. A compound as claimed in any one of claims 1 to 6 wherein the R³ substituent is an optionally substituted saturated 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N.
8. A compound as claimed in any one of claims 1 to 7 wherein X₁ represents a direct bond.
9. A compound as claimed in any one of claims 1, 5 to 8 wherein R² represents C₃₋₇cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1) wherein said R² substituent is substituted with at least one substituent selected from

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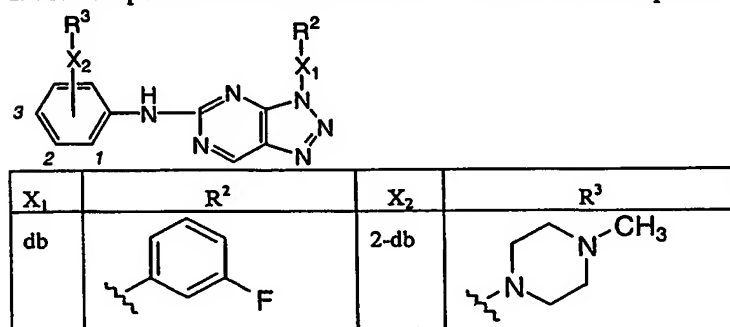
C₁₋₆alkyl substituted with NR⁶R⁷; C₂₋₆alkenyl or C₂₋₆alkynyl, each substituted with NR⁶R⁷; polyhaloC₁₋₆alkyl substituted with NR⁶R⁷; C₁₋₆alkyloxy substituted with NR⁶R⁷; polyhaloC₁₋₆alkyloxy substituted with NR⁶R⁷; or NR⁶R⁷.

- 5 10. A compound as claimed in any one of claims 1, 5, 6, 8 or 9 wherein R³ represents a 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, or a 9- or 10-membered bicyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said R³ substituent is substituted with at least one substituent selected from C₁₋₆alkyl substituted with NR⁶R⁷; C₂₋₆alkenyl or
10 C₂₋₆alkynyl, each substituted with NR⁶R⁷; C₁₋₆alkyloxy substituted with NR⁶R⁷; or NR⁶R⁷.

11. A compound as claimed in any one of claims 1, 5, 6, 7, 8 or 10 wherein R² represents C₃₋₇cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle
15 containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1), wherein said R² substituent is substituted with at least one substituent selected from halo; polyhaloC₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxy-
C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷,
20 -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhalo-C₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸.

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12. A compound as claimed in claim 1 wherein the compound is selected from

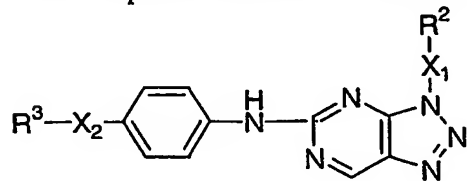


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X ₁	R ²	X ₂	R ³
db		2-db	
db		2-db	
db		2-db	
db		2-db	
db		3-db	
db		2-db	
db		3-NH	
db		2-db	
db		3-db	

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

13. A compound as claimed in claim 1 wherein the compound is selected from



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X_1	R^3	$-X_2-R^3$
db		
db		
db		
db		
db		
db		
db		

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

5 14. A compound as claimed in any one of claims 1 to 13 for use as a medicine.

15. The use of a compound as defined in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3.

10

16. The use of a compound as defined in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or the treatment of bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann

15 Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with

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tangles and calcification, Downs syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late complication of viral infections in the central nervous system), inflammatory diseases, depression, cancer, dermatological disorders, neuroprotection, schizophrenia, pain.

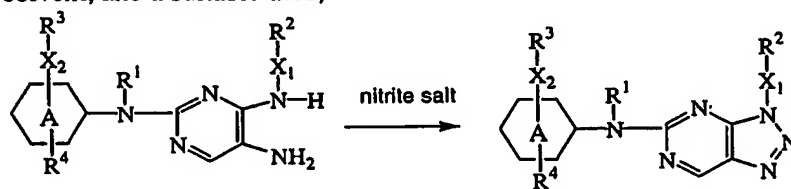
17. The use of a compound as claimed in claim 16 for the prevention or the treatment of Alzheimer's disease; diabetes; cancer; inflammatory diseases; bipolar disorder; depression; pain.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 13.

19. A process for preparing a pharmaceutical composition as claimed in claim 18 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 13 is intimately mixed with a pharmaceutically acceptable carrier.

20

20. A process for preparing a compound as claimed in claim 1, characterized by a) cyclizing an intermediate of formula (II) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,



(II)

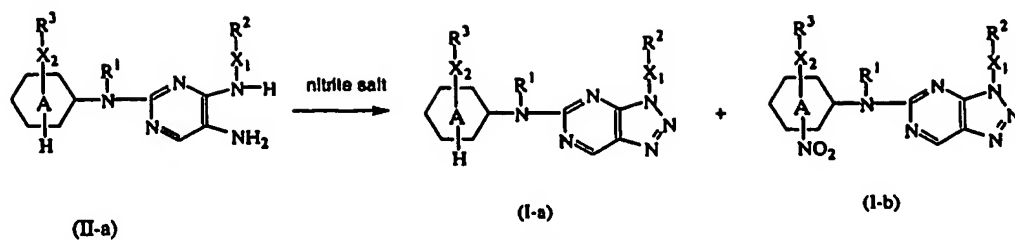
(I)

25

wherein ring A, R¹ to R⁴, X₁ and X₂ are as defined in claim 1;

b) cyclizing an intermediate of formula (II-a) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,

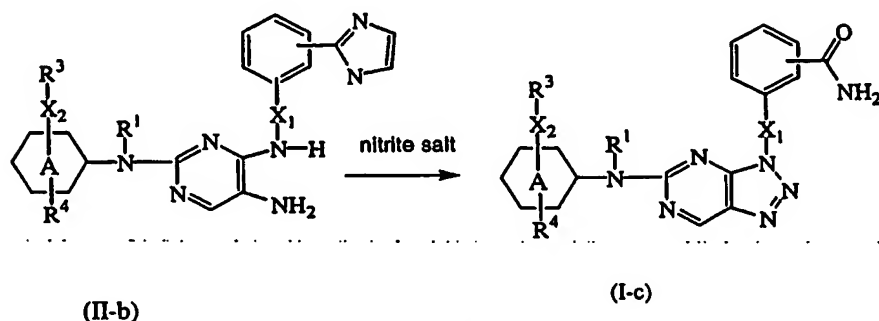
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wherein ring A, R^1 to R^3 , X_1 and X_2 are as defined in claim 1;

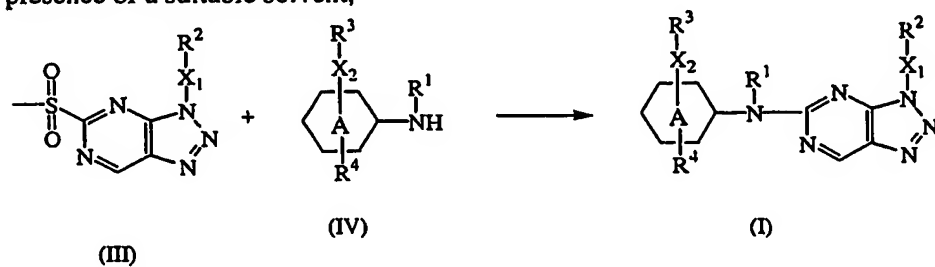
c) cyclizing an intermediate of formula (II-b) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,

5



wherein ring A, R^1 , R^3 and R^4 , X_1 and X_2 are as defined in claim 1;

d) reacting an intermediate of formula (III) with an intermediate of formula (IV) in the presence of a suitable solvent,

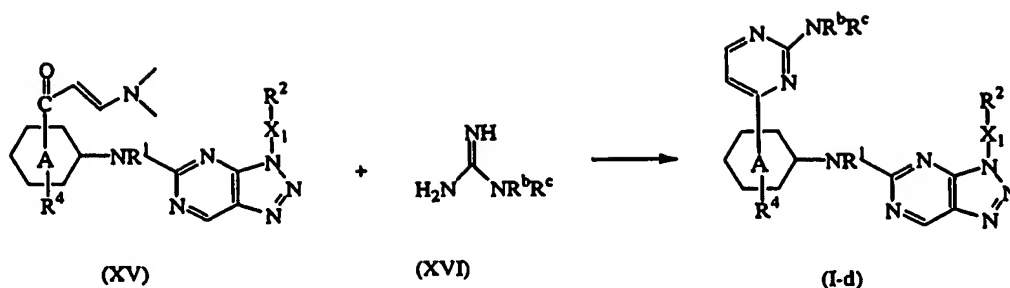


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wherein ring A, R^1 to R^4 , X_1 and X_2 are as defined in claim 1;

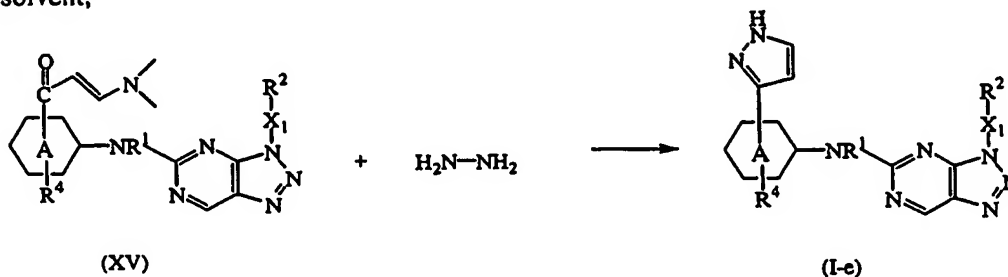
e) reacting an intermediate of formula (XV) with an intermediate of formula (XVI), wherein R^b represents hydrogen, C_{1-4} alkyl or cyano, and R^c represents hydrogen or C_{1-4} alkyl, in the presence of a suitable solvent and a suitable salt

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wherein ring A, R¹, R², R⁴ and X₁ are as defined in claim 1;

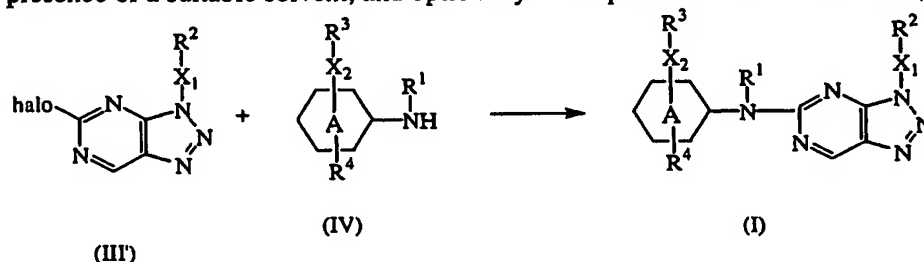
f) reacting an intermediate of formula (XV) with hydrazine in the presence of a suitable solvent,



5

wherein ring A, R¹, R², R⁴ and X₁ are as defined in claim 1;

g) reacting an intermediate of formula (III') with an intermediate of formula (IV) in the presence of a suitable solvent, and optionally in the presence of a suitable base,



10 wherein ring A, R¹, R², R³, R⁴, X₁ and X₂ are as defined in claim 1;

or, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a

15 therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, quaternary amines or *N*-oxide forms thereof